Submitted by:
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22 Dec 2014
NCCN Guidelines® Panel: Melanoma

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully request the NCCN Melanoma Panel to review the enclosed data and consider inclusion of OPDIVO® (nivolumab) for the treatment of unresectable or metastatic melanoma.[1,2,3,4,5] These data are being submitted in response to standing request from NCCN for new clinical data.

Specific Changes: In section ME-E, I respectfully request that OPDIVO® be added as a preferred regimen for the treatment of unresectable or metastatic melanoma for patients previously treated with Yervoy® (ipilimumab), regardless of BRAF status (NCCN Category 1).

For your review and consideration, please also find the attached data for the use of OPDIVO® in the first line treatment of patients with advanced metastatic melanoma without a BRAF mutation.

FDA Clearance:

The FDA approved OPDIVO® (nivolumab) on 22 Dec 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.[1]

Rationale for Proposed Change:

In support of the requested change, **FDA approval was based on a Phase 3 registrational randomized trial** in patients with advanced melanoma who had progressed after ipilimumab therapy (if BRAF V600 mutation positive, had also progressed on BRAF inhibitor therapy).[2] Patients were randomized 2:1 to receive nivolumab (3 mg/kg, Q2W) or investigator's choice of chemotherapy (ICC: dacarbazine [1000 mg/m^2 Q3W] or carboplatin [AUC 6] - paclitaxel [175mg/m^2] Q3W) until disease progression or unacceptable toxicity. The planned interim analysis for co-primary endpoint of ORR included the first 120 patients treated with nivolumab and 47 patients treated with ICC, all with ≥6 months of follow up. The other co-primary endpoint, OS in nivolumab vs ICC, had not taken place at the time of interim ORR analysis.

- The ORR (central review, RECIST v1.1) was 32% (95% CI: 24, 41) in the nivolumab group and 11% (95% CI: 4, 23) in the ICC group. Median time to response was 2.1 mo (range: 1.6, 7.4 mo) in the nivolumab group and 3.5 mo (range: 2.1, 6.1 mo) in the ICC group. Median DOR had not yet been reached in the nivolumab group (range: 1.4+, 10+ mo) and was 3.6 mo (range: 1.3+, 3.5 mo) in the ICC group.
- Drug-related AEs were reported in 68% of patients in nivolumab group and 79% of patients in ICC group. Of these 9% and 31% AEs were grade 3-4 for the nivolumab and ICC groups, respectively.

Additional support included for FDA approval was based on a Phase 1b trial[3,4]: This dose escalation (nivolumab monotherapy, 0.1 mg/kg to 10 mg/kg), cohort expansion study in previously treated advanced melanoma patients (N = 107) has a median follow-up of 55 months (range: 32, 70 mo).

- Median OS was 17.3 months across all doses and 20.3 months at 3 mg/kg. Overall survival rates at 1 yr, 2 yr, 3 yr, and 4 yr were 63%, 48%, 42%, and 32%, respectively, across all doses.
- The ORR was 32% (34/107) and 41% (7/17), and median DOR were 23 mo and 22 mo, across all doses and at 3 mg/kg, respectively. Of the responders at all doses, 41% responses were ongoing. 44% responses were seen at the first tumor assessment at 8 weeks.
- Select AEs, of any grade, were skin (38%), gastrointestinal (19%), endocrinopathies (14%), hepatic (7%), infusion reactions (6%), pulmonary (4%), and renal (2%).

Evidence for the first line use in BRAF wild-type patients is from a **Phase 3, randomized, double-blind, active-controlled trial that met the primary endpoint of overall survival.**[5] Previously untreated patients with stage III or IV melanoma, without a BRAF mutation and ECOG PS 0 or 1, were randomized 1:1 (N = 410) to receive nivolumab (3 mg/kg, Q2W) or dacarbazine (1000 mg/m^2, Q3W).

- Significant benefit was seen with respect to OS in nivolumab group (HR for death, 0.42 [99.79% CI: 0.25 to 0.73, $P < .001$]); 1-yr OS rate, 72.9% vs 42.1%; median OS, not reached yet for nivolumab vs 10.2 mo for dacarbazine.
- Grade 3 or 4 select AEs in nivolumab group were diarrhea and elevated ALT (1% each). Discontinuations due to AEs were lower in nivolumab group (6.8% vs 11.7%).

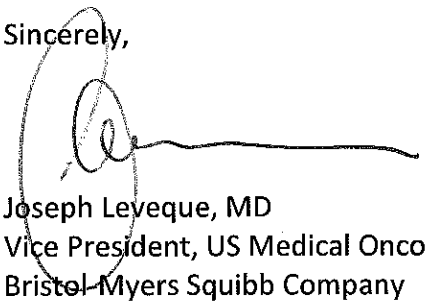
The following supportive resources are included for your review (copyright paid where applicable):

1. OPDIVO Prescribing Information
2. Weber J, Minor D, D'Angelo SP, et al. Oral presentation at the European Society for Medical Oncology (ESMO) Congress, 26-30 Sep 2014; Madrid, Spain.
3. Topalian SL, Sznol M, McDermott DF, et al. J Clin Oncol. 2014; 32:1020-1030.
4. Hodi FS, Kluger HM, Sznol M, et al. Oral presentation at the Society for Melanoma Research (SMR), 2014 International Congress; 13-16 November 2014; Zurich, Switzerland.
5. Robert C, Long G, Brady B et. al. N Engl J Med. 2014; 10.1056/NEJMoa1412082.

We acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of these publications/ presentations.

Thank you for your consideration of this request. Below is my contact information should you need to contact me for any additional information.

Sincerely,



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